Remarks

Claims 1 and 4-15 are pending in this application, claims 10-15 having been withdraw from consideration. By this Amendment, claims 1, 4-8 and 10-13 are amended to more clearly set forth the subject matter therein and to correspond more closely with the elected invention, and claims 2 and 3 are canceled. These amendments and claim cancellations are made without prejudice to or disclaimer of the subject matter therein. Support for the amendments to can be found in the specification as originally filed and in claims 1, 4-8 and 10-13 as originally filed. No new matter is added by these amendments.

I. Scope of the Elected Invention

Applicants confirm the election of Group I, claims 1-9, as indicated in the May 9, 2007, Response to Restriction Requirement. Applicants further confirm the elections of species made in that Response as follows:

Species A: R is a C_{3-10}heterocycloalkyl group;

Species B: R^1 is a C_{6-10} aryl group having 2 substituents R^a;

Species C: each R^a is independently a C_{1-6} alkyl group or a halogen; and

Species D: N-hydroxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-2-(4'-tetrahydropyranyl)-acetamide.

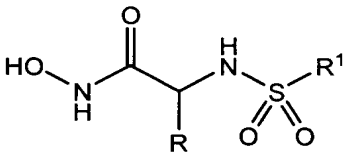
As previously discussed, these elections read on at least original claims 1, 2 and 4-15, and at least original claims 1, 6, 10 and 11 are generic.

II. Claim Rejection Under 35 U.S.C. §102

A. Jacobsen et al.

In the Office Action, claims 1-4 are rejected under 35 U.S.C. §102(b) over U.S. Patent No. 5,712,300 to Jacobsen et al. Applicants respectfully traverse this rejection with respect to amended claims 1 and 4, claims 2 and 3 having been canceled herein.

Amended independent claim 1 sets forth a "compound of formula I:

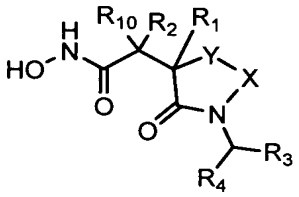


FORMULA I

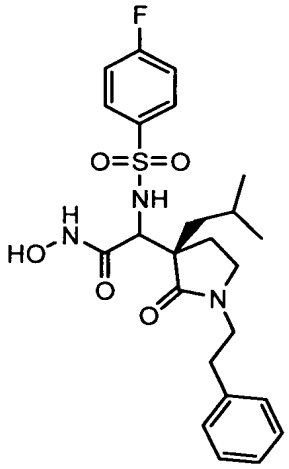
or a pharmaceutically acceptable salt or mixture thereof, wherein: R^1 is selected from the group consisting of C_{6-10} aryl groups, said aryl groups optionally substituted with 1 to 3 groups of R^a; R^a is selected from the group consisting of C_{1-6}alkyl and halogen groups; and R is selected from the group consisting of C_{3-10} heterocycloalkyl groups." Claim 4 depends from claim 1 and incorporates all of the limitations thereof.

In order to anticipate a claimed invention, a reference must disclose, in specific embodiments, all of the limitations of the claimed invention. That is, a prior art reference anticipates a claimed invention only where all claimed elements of the claimed invention are disclosed, either expressly or inherently, in the reference. Scripps Clinic & Research Foundation v. Genentech, Inc., 927 F.2d 1565, 1576, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991); In re Marshall, 577 F.2d 301, 198 USPQ 344 (CCPA 1978). Jacobsen does not disclose, in specific embodiments, compounds or pharmaceutically acceptable salts thereof as claimed in claim 1 or its dependent claim, and thus cannot anticipate claims 1 and 4.

The Jacobsen patent discloses and claims hydroxamic acid derivatives of the formula I (hereafter "formula Jacobsen I") and pharmaceutically acceptable salts thereof.



The compounds disclosed, both generally and specifically, in Jacobsen require that a lactam ring be present. *See generally* Jacobsen. Exemplary Jacobsen compounds include those in which R_2 is $NHSO_2R_5$ and R_5 is an optionally substituted aryl, which yields compounds such as that of Example 92:



(*see* Jacobsen, col. 104, lines 28-60).

The Office Action takes the position that Jacobsen anticipates the claimed compounds based on the disclosure of compounds such as that of Example 92. Applicants respectfully disagree. Jacobsen does not disclose, in discrete embodiments, all of the elements of independent claim 1. *See generally* Jacobsen.

The compounds of FORMULA I include substituent R at the position of formula Jacobsen I's required lactam ring, but the R substituent of the claimed compounds cannot be a lactam ring, which must include in the ring structure the –NHC(O)- of a lactam. *See generally* Jacobsen. That is, while the R substitutent may be a C_{3-10} heterocycloalkyl group, R cannot be a lactam ring because the claimed C_{3-10} heterocycloalkyl groups are not substituted with oxo or carboxy groups or their salts.

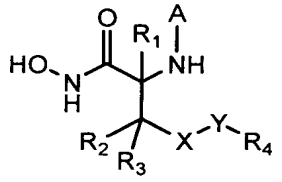
Thus, the claimed compounds of FORMULA I cannot possess a required feature of the compounds disclosed in Jacobsen. Because Jacobsen requires features that are not present in the claimed compounds and does not disclose all of the limitations of independent claim 1 as amended, it is respectfully submitted that amended claims 1 and 4 are patentable over Jacobsen. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

B. Almstead et al.

In the Office Action, claims 1-4 are rejected under 35 U.S.C. §102(b) over U.S. Patent No. 6,218,389 to Almstead et al. Applicants respectfully traverse this rejection with respect to amended claims 1 and 4, claims 2 and 3 having been canceled herein.

Amended independent claim 1 is as set forth above, and claim 4 depends from and incorporates all of the limitations of independent claim 1.

The Almstead patent discloses and claims compounds of structural formula (I)



(hereinafter "formula Almstead I"), in which A may be SO_2Ar (Ar may be an optionally substituted aromatic group), R_1 may be hydrogen, X and Y may be direct bonds, and R_2, R_3 and R_4 are independently chosen from hydrogen and optionally substituted groups chosen from alkyl, aryl, heteroaryl, aryl-alkyl, alkoxy-alkyl, heterocycle and heterocycle alkyl, and any two of R_2, R_3 and R_4 may be taken together to form a ring. Exemplary Almstead compounds include those set forth in Example 6: N-hydroxy-α-[(4-methoxyphenyl)sulfonylamino]-tetrahydro-4-methylthio-2H-pyran-4-acetamide, N-hydroxy-α-[(4-methoxyphenyl)sulfonylamino]-tetrahydro-4-methylthio-2H-thiopyran-4-acetamide, N-hydroxy-α-[(4-methoxyphenyl)sulfonylamino]-tetrahydro-4-methylthio-1-methyl-piperidine-4-acetamide and N-hydroxy-α-[(4-bromophenyl)sulfonylamino]-tetrahydro-4-methylthio-cyclohexane-4-acetamide. *See* Almstead, col. 26, lines 52-67.

The Office Action takes the position that Almstead anticipates the claimed compounds based on the disclosure of compounds such as those of Example 6. Applicants respectfully disagree. Almstead does not disclose, in discrete embodiments, all of the elements of independent claim 1. *See generally* Almstead.

The compounds of FORMULA I include substituent R at the position of formula Almstead I's required carbon having R_2, R_3 and X-Y-R_4 groups, and substituent R^1 at the position of formula Almstead I's Ar, when A is SO_2Ar. The substituent R as claimed is a C_{3-10} heterocycloalkyl group and the substituent R^1 is a C_{1-6} aryl optionally substituted with 1 to 3 groups R^a, which each may be C_{1-6}alkyl or halogens. Almstead does not teach, in specific embodiments, compounds in which one of Almstead's R_2, R_3 and X-Y-R_4 groups is hydrogen and the other two of Almstead's R_2, R_3 and X-Y-R_4 groups form a C_{3-10} heterocycloalkyl group and in which Almstead's A is SO_2Ar and Ar is a C_{1-6} aryl

optionally substituted with 1 to 3 groups C_{1-6}alkyl or halogen groups. *See generally* Almstead.

Thus, Almstead does not disclose all of the limitations of independent claim 1; it is respectfully submitted that claims 1 and 4 are patentable over Almstead. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

III. Claim Rejection Under 35 U.S.C. §103

In the Office Action, claims 1-9 are rejected under 35 U.S.C. §103(a) over U.S. Patent No. 5,712,300 to Jacobsen et al. and U.S. Patent No. 6,218,389 to Almstead et al. Applicants respectfully traverse this rejection with respect to claims 1 and 4-9 as amended, claims 2 and 3 having been canceled herein.

Amended independent claim 1 is as set forth above. Claims 4-9 depend, directly or indirectly, from claim 1 and incorporate all of the limitations thereof.

As discussed above, neither the Jacobsen patent nor the Almstead disclose, in discrete embodiments, substituent R of claimed FORMULA I. Applicants respectfully submit that neither reference, nor their combination, teaches or suggests at least substituent R of claimed FORMULA I.

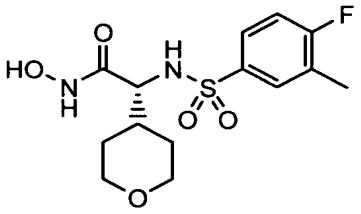
The Jacobsen patent requires a lactam ring in the position of the R substituent of claimed FORMULA I. Such a lactam ring is not a C_{3-10} heterocycloalkyl group, as set forth in claim 1, because the claimed C_{3-10} heterocycloalkyl group does not include any oxo or carboxyl group substituents and so cannot include the required –NHC(O)- of a lactam ring. *See generally* Jacobsen. In addition, Jacobsen does not teach or suggest any alternative structures at the R position, but merely requires the inclusion of a lactam ring. *See generally* Jacobsen. Thus, the claimed C_{3-10} heterocycloalkyl group would not have been obvious over the teachings of Jacobsen.

The Almstead patent broadly teaches a wide variety of substituents at the position of the R substituent of claimed FORMULA I. *See generally* Almstead. At this position, a range of substituted and unsubstituted groups may be selected for each of formula Almstead I's R_2, R_3 and X-Y-R_4 groups, with little guidance for appropriate choices and combinations. Similarly, Almstead teaches that its Ar groups, as part of groups in the A

position, may be monocyclic or bicyclic, aromatic or heteroaromatic, and substituted or unsubstituted, with little guidance for appropriate choices and combinations.

Nowhere in Almstead is there a teaching or suggestion of compounds in which one of Almstead's R_2, R_3 and X-Y-R_4 groups is hydrogen and the other two of Almstead's R_2, R_3 and X-Y-R_4 groups form a C_{3-10} heterocycloalkyl group and in which Almstead's A is SO_2Ar and Ar is a C_{1-6} aryl optionally substituted with 1 to C_{1-6}alkyl or halogen groups. *See generally* Almstead. These variables in Almstead are described in terms far broader than the descriptions of R and R^1 as originally claimed, and the variable R_1 in the formula Almstead I is limited to H in the claimed compounds. The narrowing of the variables in Almstead to the claimed compounds would not have been easily envisioned by one of skill in the art from the disclosures of the reference.

For example, the specific compound of Species D elected by Applicants is N-hydroxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-2-(4'-tetrahydropyranyl)-acetamide:



In order to arrive at this compound from the teachings of Almstead, the following choices would be necessary:

(1) A = SO_2Ar (from SO_2Ar, COAr, CONHAr and PORAr);

(2) Ar = phenyl, with the additional elections of 2 substituents (from the possibilities of 0-5 substitution positions) that are F and CH_3, each chosen from the general disclosure that "[p]referred substituents include (for example) alkyl, alkenyl, alkoxy, hydroxyl, oxo, nitro, amino, aminoalkyl ..., cyano, halo, carboxy, alkoxyaceyl ..., thiol, aryl, cycloalkyl, heteroalkyl, heterocycloalkyl ..., imino, thioxo, hydroxyalkyl, aryloxy, arylalkyl, and combinations thereof." The choice of the 4 and 3 positions of the F and CH_3 substituents would also necessary;

(3) R_1 = hydrogen (from alkyl or hydrogen);

(4) the stereochemistry of the carbon to which R_1 is attached is (*R*);

(5) X = a bond;

(6) Y = a bond;

(7) R_4 = hydrogen (from hydrogen, alkyl, aryl, heteroaryl, aryl-alkyl, alkoxy-alkyl, heterocycle, and heterocycle alkyl, which may be substituted or unsubstituted, and R_4 may form a ring with either R_2 or R_3);

(8) R_2 and R_3 are chosen from hydrogen, alkyl, aryl, heteroaryl, aryl-alkyl, alkoxy-alkyl, heterocycle, and heterocycle alkyl, which may be substituted or unsubstituted, to form a ring; and

(9) the ring formed by R_2 and R_3 is a heterocycle, specifically a 4'-tetrahydropyranyl.

Because Almstead provides only broad disclosures without specific guidance for the numerous choices necessary to arrive at just one of the claimed compounds, one of ordinary skill in the art would not easily envision the claimed compounds, based on Almstead's teachings. Rather, one of ordinary skill would have to pick and choose, with little guidance, from the broadly disclosures of each of A, Ar, R_2, R_3, X, Y and R_4 to arrive at the compounds of FORMULA I as claimed. Thus, the claimed compounds would not have been obvious over the teachings of Almstead.

The claimed compounds would also not have been obvious from the combination of Jacobsen and Almstead. In order to achieve the R substituent of the claimed compounds, one would have to replace Jacobsen's lactam, contrary to the requirements of Jacobsen, with a group prepared by a narrowing of Almstead's R_2, R_3 and X-Y-R_4 groups to a hydrogen and a C_{3-10} heterocycloalkyl group, with little guidance from Almstead, as discussed above.

In addition, the Jacobsen and Almstead merely that their compounds are metalloprotease inhibitors. *See generally* Jacobsen, Almstead. However, the references only refer to mammalian, specifically human, metalloproteases, particularly matrix metalloproteases that act on substrates such as collagen and other extra-cellular matrix proteins. *See* Jacobsen, col. 17, line 47 – col. 10, line 26; Almstead, col. 1, lines 24-36; col. 11, line 58 – col. 15, line 15. In contrast, anthrax lethal factor is a bacterial metalloprotease, which acts within cells on a different type of protein substrate, specifically mitogen-activated protein kinase kinases (MKKs). A skilled artisan would have no reason to expect that inhibitors of the former, which act on extra-cellular matrix

proteins, would also be active against other metalloproteases that act on intracellular protein substrates.

For at least these reasons, independent claim 1 and its dependent claims 4-9 would not have been obvious over the teachings of Jacobsen and Almstead, individually or in combination. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

IV. Conclusion

In view of these amendments and arguments, Applicants respectfully submit that this application is in condition for allowance. The Examiner is invited to contact the undersigned at the telephone number set forth below, should she believe that anything further is necessary to place this application in even better form for allowance.

Please charge Deposit Account No. 13-2755 for any fees due in connection with this Amendment. If any time extensions are needed for the timely filing of this Amendment, Applicants petition for such extensions and authorize the charging of Deposit Account No. 13-2755 for the necessary fees.

Respectfully submitted,

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on the date appearing below.

MERCK & CO., INC.
By _____ Date 10/15/2007

By _____
June M. Lake
Registration No. 51,156
Attorney for the Applicants

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Attachment: Petition for Extension of Time